Bone mineral density in postmenopausal women with and without breast cancer

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Summary

Objective: The values of bone mineral density (BMD) were compared in postmenopausal women with and without breast cancer. **Methods:** A cross-sectional study was conducted, including 51 breast cancer survivors (BCS) and 71 women without breast cancer, who were non-users of hormone therapy, tamoxifen, or aromatase inhibitors. BMD T-scores and measurements in grams per centimeter squared (g/cm^2) were obtained at the femoral neck, trochanter, Ward's triangle, and lumbar spine. Osteopenia and osteoporosis were grouped and categorized as abnormal BMD. Unconditional logistic regression analysis was used to estimate the odds ratios (OR) of abnormal BMD values as measures of association, with 95% confidence intervals (CIs), adjusting for age, years since menopause, parity, and body mass index (BMI). **Results:** The mean age of the women with and without breast cancer was 54.7 ± 5.8 years and 58.2 ± 4.8 years ($p < 0.01$), respectively. After adjusting for age, parity and BMI, abnormal BMD at the femoral neck (adjusted OR: 4.8; 95% CI: 1.5-15.4), trochanter (adjusted OR: 4.6; 95% CI: 1.4-15.5), and Ward's triangle (adjusted OR: 4.5; 95% CI: 1.5-12.9) were significantly more frequent in postmenopausal BCS than in women without breast cancer. Postmenopausal BCS had a significantly lower mean BMD at the trochanter (0.719 *vs.* 0.809 g/cm^2, $p < 0.01$) and at the Ward's triangle (0.751 *vs.* 0.805 g/cm^2, $p = 0.03$). **Conclusion:** The prevalence of abnormal BMD was higher in postmenopausal BCS than in postmenopausal women without breast cancer. Bone health requires special vigilance and the adoption of interventions should be instituted early to minimize bone loss in BCS.

Keywords: Breast cancer; menopause; bone loss; abnormal bone mineral density.

Resumo

Densidade mineral óssea em mulheres na pós-menopausa com e sem câncer de mama

Objetivo: Comparar a densidade mineral óssea (DMO) de mulheres na pós-menopausa com e sem câncer de mama. **Métodos:** Conduziu-se estudo de corte transversal, incluindo 51 mulheres com câncer de mama e 71 mulheres sem câncer de mama, não usuárias de terapia hormonal, tamoxifeno ou de inibidores da aromatase. Avaliou-se a DMO, em T-score e em gramas por centímetro quadrado (g/cm^2), no colo do fêmur, trocânter, triângulo de Wards e na coluna lombar. Osteopenia e osteoporose foram agrupadas e categorizadas como DMO alterada. Utilizou-se a análise de regressão logística não condicional para estimar o odds ratios (OR) de DMO alterada como medida de associação, com intervalo de confiança de 95% (IC 95%), ajustando-se por idade, anos de menopausa, paridade e índice de massa corpórea (IMC). **Resultados:** A média de idade de mulheres com e sem câncer de mama foi 54,7 ± 5,8 anos e 58,2 ± 4,8 anos ($p < 0,01$), respectivamente. Após ajustar por idade, paridade e IMC, DMO alterada no colo do fêmur (OR ajustado: 4,8; IC 95%: 1,5-15,4), trocânter (OR ajustado: 4,6; IC 95%: 1,4-15,5) e no triângulo de Wards (OR ajustado: 4,5; IC 95%: 1,5-12,9) foi mais frequente em mulheres com câncer de mama. Mulheres com câncer de mama apresentaram significativamente menor média de DMO no trocânter (0,719 *vs.* 0,809 g/cm^2, $p < 0,01$) e no triângulo de Wards (0,751 *vs.* 0,805 g/cm^2, $p = 0,03$). **Conclusão:** A prevalência de DMO alterada foi maior em mulheres na pós-menopausa com câncer de mama. A saúde óssea requer vigilância especial e a adoção precoce de intervenções para minimizar a perda óssea de mulheres com câncer de mama.

Unitermos: Câncer de mama; menopausa; perda óssea; densidade mineral óssea alterada.

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Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide, representing 23% (1.38 million) of the total new cancer cases in 2008[1]. Breast cancer is primarily a disease of postmenopausal women[2]. In the postmenopause, there is a reduction in serum estrogen levels leading to bone loss. Estrogen plays an important role in skeletal maintenance due to its osteoprotective action[3]. In this context, postmenopausal status is a major risk factor for low bone mineral density (BMD)[4].

Previous studies have demonstrated a relationship between a higher BMD and a higher risk for postmenopausal breast cancer[5,6]. Although the mechanism of this relationship is not fully understood, cumulative exposure to estrogen may play a role[5]. BMD may be a predictor for breast cancer risk, but breast cancer survivors (BCS) can also develop bone loss related to cancer treatment[7,8]. Chemotherapy-induced ovarian failure[7,8], aromatase inhibitor use[9,10], and a potential direct toxic chemotherapy effect on bone tissue[11] may induce and intensify bone loss in BCS. Tamoxifen use is associated with significant bone loss in premenopausal BCS. However, tamoxifen exerts a bone-protective action in women with early menopause induced by chemotherapy[12].

Premenopausal women with breast cancer undergoing chemotherapy with preserved ovarian function do not have a significant reduction in bone mass[7,8]. However, those who develop amenorrhea have a rapid and significant bone loss[7,8]. Menopausal hormone therapy may be indicated for the prevention of bone loss[13], and many women on hormone therapy at the time of breast cancer diagnosis are instructed to discontinue its use[2]. Discontinuation of hormone therapy is based on an increased risk of breast cancer recurrence[14]. This group of factors contributes to increased bone loss in postmenopausal BCS.

Previous studies have investigated BMD in postmenopausal survivors of breast cancer[15-22]. However, few studies have evaluated a group of women without breast cancer for comparison[18,19,22]. In one study, mean BMD values in postmenopausal BCS were similar to those in population-based non-BCS[18]. In contrast, the prevalence of osteoporosis in another study was 27.2% in BCS and 19.4% in women without breast cancer[19]. Furthermore, it was demonstrated that postmenopausal BCS had a higher fracture risk than cancer-free women[20].

Despite these findings, a notable proportion of postmenopausal BCS have undiagnosed abnormal BMD[15,16,19]. Considering these aspects, the present study was conducted aiming to compare BMD in Brazilian postmenopausal women with and without breast cancer

Methods

Patients

Participant selection has been previously described in detail[23]. The current sample was derived from a study that investigated menopause symptoms, sexual activity, quality of life, some cardiovascular risk factors, and BMD in BCS[23]. The present study focused on the findings of BMD in postmenopausal women with and without breast cancer.

A cross-sectional study of women undergoing routine follow-up care was conducted in the Women's Hospital of the School of Medicine of the Universidade Estadual de Campinas, Brazil. Patients who met the inclusion criteria were invited to participate in the study during outpatient consultation. Women aged 45-65 years, who were non-users of hormone therapy or tamoxifen in the last six months, and who had no history of other malignancies were invited. Only postmenopausal women who completed oncology treatment were included in this study. None of the BCS were using aromatase inhibitors. A total of 187 women were invited to participate in the study, 100 BCS and 87 without breast cancer. Among the BCS, three refused to participate in the study due to lack of time, 22 were undergoing oncology treatment, 12 were premenopausal, seven had no knowledge of time since menopause, and five did not have bone density measurements. Among women without breast cancer, two refused to participate in the study due to lack of time, four were premenopausal, and ten had no knowledge of time since menopause. Therefore, 122 postmenopausal women, 51 with breast cancer and 71 without breast cancer, constituted the present study sample.

Participants responded to an interview that assessed sociodemographic characteristics, including age, race/ethnicity, age at menarche, parity, smoking, age at menopause, and years since menopause. Clinical characteristics included body mass index (BMI) in kilograms per square meter (kg/m^2), time since breast cancer diagnosis, type of surgery, tumor stage, chemotherapy, and radiotherapy. This study was approved by the institutional review board; all participants signed an informed consent.

Bone mineral density measurement

BMD tests were ordered in the initial interview with the patient. BMD in grams per centimeter squared (g/cm^2) was measured at the femoral neck, trochanter, Ward's triangle, and the lumbar spine (L2-L4; anteroposterior plane) using a Lunar DPX device (DXA; Lunar DPX, Madison, WI, USA). BMD values were also expressed as T-scores, using the World Health Organization criteria[24]: normal: T-score ≥ -1 standard deviation (SD); osteopenia: T-score between -1 and -2.5 SDs; osteoporosis: T-score ≤ -2.5 SDs. In this study, a BMD T-score < -1 SD was considered abnormal (osteopenia and osteoporosis grouped together).

Statistical analysis

The means of descriptive continuous variables were compared between women with and without cancer using Student's *t*-test for independent samples. The frequencies of binary variables were compared by Fisher's exact test. Unconditional logistic regression analysis[25] was used to estimate the odds ratios (OR) of abnormal BMD as measures of association, with 95% confidence intervals (CIs). In these models, the independent binary variable was breast cancer (with cancer/without cancer), and the dependent binary variable was BMD, classified as normal or abnormal. The ORs were estimated as measures of the association between cancer and abnormal BMD in the femoral neck, trochanter, Ward's triangle and lumbar spine with and without adjustment for age, parity, years since menopause, and BMI in quartiles. When age and years since menopause were considered, regression models could not be fitted because of the strong collinearity between these variables. The ORs adjusted for age, parity, and BMI, and adjusted for years since menopause, parity, and BMI were estimated. When bone density (g/cm^2) was regarded as a continuous variable, linear regression models[26] were used to compare the population means between women with and without cancer adjusting for covariates. All analyses were performed using the SAS version 9.2 software. The significance level was set at 5%.

Results

The mean age of women with breast cancer was 54.7 ± 5.8 years and 58.2 ± 4.8 years for those without breast cancer ($p < 0.01$). The mean BMI was 27.5 ± 5.2 kg/m^2 and 30.2 ± 5.7 kg/m^2 for women with and without breast cancer ($p < 0.01$), respectively. The mean age at menopause was 47.1 ± 5.0 years for women with breast cancer and 47.4 ± 4.9 years for women without breast cancer ($p = 0.98$). Bone density measurement was performed from one to two months after the first interview. Other characteristics are shown in Table 1. In the breast cancer group, the mean time since breast cancer diagnosis was 67.9 ± 53.1 months. A little over half of the postmenopausal BCS (52.9%) underwent mastectomy, and 47.1% underwent breast-conserving therapy. Approximately 72% of women underwent chemotherapy, 76.5% underwent radiation therapy, and 60.8% underwent chemotherapy and radiation therapy. Distribution according to tumor stage was (n, %): 0 (4, 7.8%), I (7, 13.7%), II (31, 60.8%), and III (9, 17.7%).

In the unadjusted analysis, the results in Table 2 show that postmenopausal BCS had a significantly higher prevalence of abnormal BMD at the femoral neck, trochanter, and Ward's triangle than women without breast cancer. After adjusting for age, parity, and BMI, abnormal BMD at the femoral neck (adjusted OR: 4.8; 95% CI: 1.5-15.4), trochanter (adjusted OR: 4.6; 95% CI: 1.4-15.5), and Ward's triangle (adjusted OR: 4.5; 95% CI: 1.5-12.9) was significantly more frequent in postmenopausal BCS than in women without breast cancer. After adjusting for years since menopause, parity, and BMI, the prevalence of abnormal BMD at the femoral neck, trochanter, and Ward's triangle remained significantly higher in postmenopausal BCS. In unadjusted and adjusted analysis, there was no significant difference in the prevalence of abnormal lumbar spine (L2-L4) BMD between BCS and women without breast cancer.

Figure 1 displays the mean BMD (g/cm^2) of postmenopausal BCS and women without breast cancer. On analysis adjusted for age, parity, and BMI, BCS showed a significantly lower mean BMD at the trochanter (0.719 *vs.* 0.809 g/cm^2, $p < 0.01$) and Ward's triangle (0.751 *vs.* 0.805 g/cm^2, $p = 0.03$). After adjusting for years since menopause, parity, and BMI, BCS had a significantly lower mean BMD at the trochanter ($p < 0.01$), and Ward's triangle ($p = 0.03$).

Discussion

This study aimed to compare BMD in women with and without breast cancer. Few studies have investigated BMD in postmenopausal BCS, in comparison to a group of postmenopausal women without breast cancer. Based on BMD

Table 1 – Sociodemographic and clinical features of postmenopausal women with and without breast cancer

Characteristics	With cancer (n = 51)	Without cancer (n = 71)	p-value
Age (years)	54.7 ± 5.8	58.2 ± 4.8	< 0.01[a]
Age at menarche (years)	13.1 ± 1.8	13.1 ± 1.9	0.85[a]
Body mass index (kg/m^2)	27.5 ± 5.2	30.2 ± 5.7	< 0.01[a]
Age at menopause (years)	47.1 ± 5.0	47.4 ± 4.9	0.98[a]
Years since menopause	7.4 ± 5.2	10.6 ± 5.3	< 0.01[a]
Race (% white women)	21.6	32.4	0.22[b]
Parity (% nulliparous)	17.7	4.2	0.03[b]
Smokers (%)	13.7	5.6	0.22[b]

Data are expressed as mean ± SD unless otherwise specified. [a] Student's *t*-test for independent samples; [b] Fisher's exact test.

Table 2 – Comparison of prevalence of abnormal bone mineral density (T-score < - 1 SD) of postmenopausal women with and without breast cancer

Site	With cancer n (%)	Whitout cancer n (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Femoral neck					
Normal	32 (62.8)	57 (80.3)	1.00	1.00	1.00
Abnormal	19 (37.2)	14 (19.7)	2.4 (1.1-5.5)	4.8 (1.5-15.4)	3.8 (1.2-11.5)
Trochanter					
Normal	25 (59.5)	47 (85.5)	1.00	1.00	1.00
Abnormal	17 (40.5)	8 (14.5)	4.0 (1.5-10.5)	4.6 (1.4-15.5)	4.6 (1.3-15.1)
Ward's triangle					
Normal	17 (40.5)	34 (61.8)	1.00	1.00	1.00
Abnormal	25 (59.5)	21 (38.2)	2.4 (1.0-5.4)	4.5 (1.5-12.9)	3.8 (1.3-10.7)
Lumbar spine (L2-L4)					
Normal	22 (43.1)	40 (56.3)	1.00	1.00	1.00
Abnormal	29 (56.9)	31 (43.7)	1.7 (0.8-3.5)	1.2 (0.5-2.9)	1.5 (0.6-3.5)

SD, standard deviation; OR, odds ratio; CI, confidence interval, [a] OR estimates adjusted for age, parity and body mass index in quartiles; [b] OR estimates adjusted for years since menopause, parity and body mass index in quartiles.

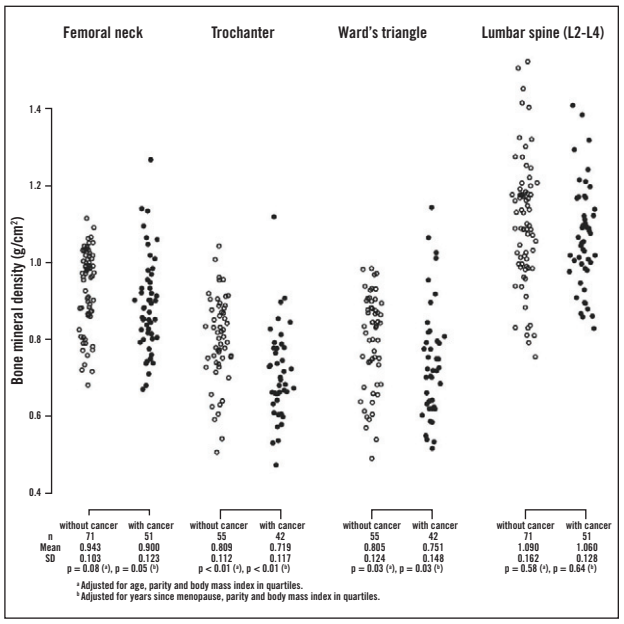

Figure 1 – Comparison of mean bone mineral density (g/cm²) in postmenopausal women with and without breast cancer.

T-scores, it was observed that abnormal BMD at the femoral neck, trochanter, and Ward's triangle was significantly more frequent in BCS than in women without breast cancer. Furthermore, BCS had a significantly lower mean BMD (g/cm²) at the trochanter and Ward's triangle.

In this case study, it was observed that the prevalence of abnormal BMD in postmenopausal BCS was higher at the Ward's triangle (59.5%), and lumbar spine (56.9%). In another study, including only postmenopausal BCS with a mean age of 54 years and 36.6% of tamoxifen users, it was observed that 56.3% of the participants had abnormal BMD at the lumbar spine[15]. The findings of these authors[15] were similar to the present results regarding the high prevalence rate of abnormal BMD at the lumbar spine (56.9%), although the participants of the present cohort were non-users of tamoxifen. Other studies have also reported a high frequency of abnormal BMD at the lumbar spine[19,21,22]. The lumbar spine and Ward's triangle have a high content of trabecular bone. A higher frequency of abnormal BMD at these bone sites may be related to a greater sensitivity of trabecular bone to estrogen deficiency[27]. This is a characteristic of postmenopausal women who do not use hormone therapy.

Few studies comparing BMD between postmenopausal BCS and women without breast cancer have been identified[18,19,22]. Based on cross-sectional data[18], BMD Z-scores of BCS were investigated. This study found that postmenopausal patients who had not received adjuvant therapy had higher whole body BMD compared to age-matched women. Furthermore, the authors reported that hip and spine BMD measurements in postmenopausal BCS were similar to those in a population-based sample without breast cancer, suggesting that the treatment had caused no major deleterious effect on the BMD of BCS[18]. However, a retrospective study found that women who were postmenopausal at the time of breast cancer diagnosis and receiving adjuvant chemotherapy had lower BMD Z-scores at the total hip, femoral neck, trochanter, and lumbar spine than those who had not received chemotherapy[17], indicating a potential detrimental effect of adjuvant therapy on the BMD of postmenopausal women.

In another study[22], BMD was compared between a BCS group with chemotherapy-induced amenorrhea and a premenopausal control group without breast cancer.

The authors of this study observed that significantly more BCS had low spine BMD based on T-scores[22]. In the Women's Health Initiative Observational Study (WHI-OS), data on the prevalence of low bone mass was reported in a large cohort of postmenopausal BCS, compared to cancer-free women[19]. In the WHI-OS, the frequency of osteoporosis was 27.2% in postmenopausal BCS and 19.4% in cancer-free women. A comparison of BMD T-scores in postmenopausal BCS and in women with no history of breast cancer, adjusting for covariables, except menopausal hormone therapy, showed BCS with a significantly higher prevalence of osteoporosis in the total hip, total body, and at any site[19]. In the present study, the prevalence of abnormal BMD T-scores at the femoral neck, trochanter, and Ward's triangle was higher in BCS in adjusted and unadjusted analyses. The mean BMD (g/cm^2) at the trochanter and Ward's triangle was higher among postmenopausal non-BCS, adjusting for potential confounding variables (age, years since menopause, parity, BMI). In the WHI-OS, when menopausal hormone therapy was added as a covariate, the difference in the prevalence of osteoporosis between women with and without breast cancer was no longer significant[19]. Participants in the present study were not using hormone therapy, thus it was not possible to adjust for this variable.

Differences observed between the present findings and results of other studies may be related to the age difference between the participants, bone sites investigated, and variables evaluated. In the WHI-OS, a low BMD and high prevalence of osteoporosis in BCS occurred, especially because of lower hormone therapy use by these women[19]. The present study included women who did not take tamoxifen or aromatase inhibitors, since the aim at the time of study design was to gain knowledge about BMD in BCS who were not receiving any hormone therapy.

From the present findings and previous studies, it can be inferred that abnormal BMD is a concern for postmenopausal BCS[15-19,21,22]. Despite these findings, 77.8% of the WHI-OS postmenopausal BCS had undiagnosed osteoporosis at baseline. Thus, a considerable proportion of BCS women had no diagnosis of abnormal BMD and consequently did not receive therapy, as previously reported[16].

The findings should be interpreted considering some limitations, such as the cross-sectional study design and a lack of information about chemotherapy regimen. The immunohistochemical profile of tumors in BCS, which could have allowed the investigation of a relationship between hormone receptor status and BMD, was not included. Physical activity, and calcium, caffeine, and alcohol consumption were not investigated. However, there was inconsistent evidence of an association between current physical activity or calcium intake and BMD in a systematic review[4]. In this review, there was fair evidence that current caffeine intake was not associated with BMD, and that moderate alcohol consumption was not associated with lower BMD[4].

To the authors' knowledge, this was the first study conducted in Latin America investigating BMD in postmenopausal BCS. The existence of a control group of women with similar menopausal status, i.e., postmenopausal women with no history of breast cancer, is highlighted. Despite some differences between both groups, the comparisons between BMD were adjusted for potential confounding variables.

The current guidelines of the American Society of Clinical Oncology recommend the use of aromatase inhibitors in postmenopausal BCS with hormone receptor-positive tumors during adjuvant therapy as an initial treatment, or sequential or extended treatment after tamoxifen use[28]. Although further studies are still required, a recent randomized, placebo-controlled, double-blinded trial in healthy postmenopausal women has demonstrated that exemestane reduced the relative incidence of invasive breast cancers by 65%[29]. This group of data suggests that the use of aromatase inhibitors will become increasingly more frequent. In this context, the prevalence of abnormal BMD in BCS may be higher in the future than in the present study. In BCS, there is a need for increased vigilance of bone health, especially in postmenopausal women.

Conclusion

In conclusion, the authors believe that these results are of interest to healthcare professionals involved in the management of women with breast cancer. The prevalence of abnormal BMD was higher in postmenopausal BCS than in postmenopausal women without breast cancer. Bone health requires special vigilance and the adoption of interventions should be instituted early to minimize bone loss in BCS.

References

1. International Agency for Research on Cancer. GLOBOCAN 2008. Worldfemale. Estimated incidence by age. [cited 2012 jan 12]. Available from: http://globocan.iarc.fr/age-specific_table_r_PDF.asp?selection=221900&title=World&sex=2&type=0&stat=0&PDF=1&window=1&sort=0&submit=%A0Execute%A0).
2. Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. J Natl Cancer Inst. 2000;92:1054-64.
3. Imai Y, Kondoh S, Kouzmenko A, Kato S. Minireview: osteoprotective action of estrogens is mediated by osteoclastic estrogen receptor-alpha. Mol Endocrinol. 2010;24:877-85.
4. Waugh EJ, Lam MA, Hawker GA, McGowan J, Papaioannou A, Cheung AM, et al. Risk factors for low bone mass in healthy 40-60 year old women: a systematic review of the literature. Osteoporos Int. 2009;20:1-21.
5. Zhang Y, Kiel DP, Kreger BE, Cupples LA, Ellison RC, Dorgan JF, et al. Bone mass and the risk of breast cancer among postmenopausal women. N Engl J Med. 1997;336:611-7.
6. Chen Z, Arendell L, Aickin M, Cauley J, Lewis CE, Chlebowski R. Hip bone density predicts breast cancer risk independently of Gail score: results from the Women's Health Initiative. Cancer. 2008;113:907-15.

7. Saarto T, Blomqvist C, Välimäki M, Mäkelä P, Sarna S, Elomaa I. Chemical castration induced by adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: a randomized study in premenopausal breast cancer patients. J Clin Oncol. 1997;15:1341-7.
8. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol. 2001;19:3306-11.
9. Coleman RE, Banks LM, Girgis SI, Kilburn LS, Vrdoljak E, Fox J, et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol. 2007;8:119-27.
10. Eastell R, Adams JE, Coleman RE, Howell A, Hannon RA, Cuzick J, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol. 2008;26:1051-7.
11. Banfi A, Podestà M, Fazzuoli L, Sertoli MR, Venturini M, Santini G, et al. High-dose chemotherapy shows a dose-dependent toxicity to bone marrow osteoprogenitors: a mechanism for post-bone marrow transplantation osteopenia. Cancer. 2001;92:2419-28.
12. Vehmanen L, Elomaa I, Blomqvist C, Saarto T. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. J Clin Oncol. 2006;24:675-80.
13. The North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause. 2010;17:25-54.
14. Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol. 2009;10:135-46.
15. Twiss JJ, Waltman N, Ott CD, Gross GJ, Lindsey AM, Moore TE. Bone mineral density in postmenopausal breast cancer survivors. J Am Acad Nurse Pract. 2001;13:276-84.
16. Lindsey AM, Gross G, Twiss J, Waltman N, Ott C, Moore TE. Postmenopausal survivors of breast cancer at risk for osteoporosis: nutritional intake and body size. Cancer Nurs. 2002;25:50-6.
17. Greep NC, Giuliano AE, Hansen NM, Taketani T, Wang HJ, Singer FR. The effects of adjuvant chemotherapy on bone density in postmenopausal women with early breast cancer. Am J Med. 2003;114:653-9.
18. Crandall C, Petersen L, Ganz PA, Greendale GA. Bone mineral density and adjuvant therapy in breast cancer survivors. Breast Cancer Res Treat. 2004;88:257-61.
19. Chen Z, Maricic M, Pettinger M, Ritenbaugh C, Lopez AM, Barad DH, et al. Osteoporosis and rate of bone loss among postmenopausal survivors of breast cancer. Cancer. 2005;104:1520-30.
20. Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, et al. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. Arch Intern Med. 2005;165:552-8.
21. Twiss JJ, Gross GJ, Waltman NL, Ott CD, Lindsey AM. Health behaviors in breast cancer survivors experiencing bone loss. J Am Acad Nurse. Pract. 2006;18:471-81.
22. Winters-Stone KM, Nail L, Bennett JA, Schwartz A. Bone health and falls: fracture risk in breast cancer survivors with chemotherapy-induced amenorrhea. Oncol Nurs Forum. 2009;36:315-25.
23. Conde DM, Pinto-Neto AM, Cabello C, Sá DS, Costa-Paiva L, Martinez EZ. Menopause symptoms and quality of life in women aged 45 to 65 years with and without breast cancer. Menopause. 2005;12:436-43.
24. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. Osteoporos Int. 1994;4:368-81.
25. Hosmer DW, Lemeshow S. Applied logistic models. 2nd ed. New York: John Wiley& Sons; 2000.
26. Montgomery DC, Peck EA, Vining GG. Introduction to linear regression analysis. 4th ed. New York: John Wiley & Sons; 2007.
27. Beerthuizen R, van Beek A, Massai R, Mäkäräinen L, Hout J, Bennink HC. Bone mineral density during long-term use of the progestagen contraceptive implant Implanon compared to a non-hormonal method of contraception. Hum Reprod. 2000;15:118-22.
28. Burstein HJ, Prestrud AA, Seidenfeld J, Anderson H, Buchholz TA, Davidson NE, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol. 2010;28:3784-96.
29. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364:2381-91.